

aHUS Facts and Key Information

International aHUS Awareness Day is 24 September

Information about the Rare Disease Atypical Hemolytic Uremic Syndrome



An Outreach and Education Initiative of the aHUS Alliance (Sept 2015)

www.aHUSAlliance.org

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About aHUS

- Atypical Hemolytic Uremic Syndrome (aHUS) is a very rare, chronic and life-threatening genetic condition
- aHUS can occur at any age, with roughly 60 per cent of children affected and 40 per cent adults ²
- aHUS is caused by chronic, uncontrolled activation of the complement system, a part of the body's natural immune system ¹
- As a result, the immune system attacks the body's unhealthy and healthy cells, which can cause abnormal blood clotting and blood vessel damage ^{2,3}
- The presence of blood clots causes damage to organs, leading to heart attack, stroke, kidney failure and death ²
- Within a year of diagnosis, over half of patients will need dialysis, will have irreversible kidney damage, or will not survive ²
- The majority of patients progress to end-stage kidney failure within three years of diagnosis ^{2,5}
- Death rates amongst aHUS patients are as high as 25 per cent, and progression to end-stage kidney disease occurs in more than 50 per cent of patients ^{2,5}
- Kidneys are often transplanted in aHUS patients with permanent kidney failure, however, the disease recurs in 60 per cent of patients, and more than 90 per cent of patients experience failure of transplanted kidney ²

Diagnosis

- Atypical HUS encompasses a group of diseases that share in the clinical features of a microangiopathic hemolytic anemia associated with thrombocytopenia and renal failure. In practice there is little agreement on what defines or limits classifying someone as an aHUS patient, given the nonspecific nature of the term aHUS. aHUS clumps together a group of diseases with very different underlying pathologies. ²⁵
- The causes of aHUS are not fully understood, but in 70 per cent of cases it is associated with an underlying genetic or acquired abnormality of the complement system ¹⁰
- Doctors and their health care team must look at many factors when making a diagnosis – including clinical symptoms, lab findings, and results from more specialized tests such as gene analysis ¹¹
- During initial onset of aHUS, or during recurring episodes, tell-tale signs can be detected from lab findings relating to ⁹
 - platelet levels
 - hemoglobin and haptoglobin levels
 - creatinine levels
 - BUN (blood urea nitrogen) levels

Symptoms

- aHUS disease can be characterized by three key features:¹²
 - thrombocytopenia (low platelet count in the blood)
 - anemia (low red blood cell/platelet count in the blood)
 - kidney symptoms (starting as acute kidney failure but can progress to end-stage kidney disease)
- There are a number of symptoms secondary to kidney failure, which include ¹⁰
 - nausea and vomiting
 - confusion
 - shortness of breath (dyspnea)
 - fatigue
- In aHUS, patients present with symptoms of diarrhea, fatigue, irritability, and lethargy to a point where hospitalization is needed¹²
- The majority of patients have genetic abnormalities that impair cell surface control of complement¹⁸

Treatment

Plasma Therapy & Dialysis

- The prognosis for patients with aHUS is very poor,¹³ with existing supportive therapies unproven and unreliable
- The management of aHUS has relied on plasma infusion and plasma exchange therapies with variable results¹⁴
- To date, there have been no well-controlled trials that show plasma exchange or plasma infusion to be safe or effective in aHUS¹⁵
- In studies where the majority of patients with aHUS were treated with plasma therapy, patient outcomes were reported as being poor¹⁶
- Despite plasma exchange or plasma infusion, 65 per cent of all aHUS patients die, require dialysis, or have permanent renal damage within the first year after diagnosis⁶
- Dialysis cannot completely compensate for the loss of kidney function, and can lead to deadly infections and shortened life expectancy ¹⁷
- Complications related to plasma exchange have been reported to occur in up to 55 per cent of plasma exchange sessions in children and in 15 per cent of sessions in adults¹⁶

eculizumab

- Eculizumab has shown greater efficacy than plasma therapy in the prevention and treatment of aHUS^{16, 19}
- Experts recommend the use of eculizumab as first-line therapy in children with aHUS, and for adults with an unequivocal diagnosis of aHUS ¹⁶
- Clinicians advise that patients with native or transplanted kidneys whose aHUS recurs be treated with eculizumab ¹⁶, and that treatment be initiated as early as possible for optimal recovery of renal function¹⁹
- Switching from plasma therapy to eculizumab has been shown to improve renal function even in patients with long-lasting and stable chronic kidney disease ¹⁶
- In clinical trials, eculizumab has been proven effective in preventing blood vessel damage and abnormal blood clotting ^{20, 21}
- In June 2013, an international study in the *New England Journal of Medicine* showed aHUS patients treated with eculizumab were able to discontinue plasma infusion/exchange and dialysis therapies, and saw improved kidney function, reduced blood vessel damage and decreased risk of blood clots ²²

Access to Treatment

- As of June 2015 aHUS patients in many nations still do not have access to eculizumab, and coverage within some of those countries is further restricted: dependent on the aHUS patient's location within their nation or their individual health status.²⁶
- In September 2013, National Health Service (NHS) England recommended that eculizumab be funded for aHUS patients, following a positive reimbursement recommendation from the Clinical Priorities Advisory Group (CPAG). The final draft guidance recommending eculizumab for funding for treating aHUS was issued by the National Institute for Health and Care Excellence (NICE) in November of 2014.

Note: The aHUS Alliance wishes to extend thanks to aHUS Canada for their efforts in providing the core of facts contained in this document.

SOURCES: See our CITATIONS section later in this document.

Future aHUS Treatment?

Some Potential New Complement Inhibitors Under Investigation^{26,27} as of Aug 2015

Company	Molecule	Mechanism	Indications	Stage*
Alnylam	ALN-CC5	C5 gene knockdown	PNH	P I/II
Apellis	Compstatin® / APL-2	C3 inhibitor	PNH	P I/II
Omeros	OMS721® / MASP-2	Lectin pathway inhibitor	TMA's including aHUS	P II
Volution	Coversin®	C5 inhibitor	PNH, aHUS, Guillain Barre Syndrome	P I/II
Ra	RA101495	C5 inhibitor	PNH, initially	P I

* *Clinical Trials, Stages of Development:* <http://www.nlm.nih.gov/services/ctphases.html>

See **Alnylam's** Corporate site, regarding ALN-CC5®: <http://investors.alnylam.com/releasedetail.cfm?ReleaseID=871024>

See **Apellis'** Corporate site, regarding Compstatin®/APL-2: <http://apellis.com/portfolio-item/rare-diseases/>

See **Omeros'** Corporate site, regarding OMS721®/MASP-2: <http://www.omeros.com/pipeline/masp2.htm>

OMS721, currently in Clinical Trials: <https://clinicaltrials.gov/ct2/show/NCT02222545?term=oms721&rank=1>

See **Volution's** Corporate site, regarding Coversin®: <http://vipimmunopharma.com/coversin/>

See **Ra Pharmaceutical's** Corporate site, regarding RA101495®: <http://rapharma.com/programs.html>

aHUS Around the World

- The estimated incidence of aHUS in the USA is 2 per 1,000,000 ²⁴
- aHUS Canada estimates aHUS affects between 60 to 90 patients in Canada

aHUS Global Poll on RareConnect: Living with Atypical HUS

This survey was a joint partnership of RareConnect and the atypical HUS patient associations in multiple nations, with assistance by EURORDIS regarding the survey creation, interpretation, and publication of this infographic and the poll results. The polling was open from 17th February, 2014 to 7th March, 2014. Conducted in 6 languages, there were a total of 214 responses from 17 countries.

View full Poll Results: <http://bit.ly/1UIDpS5>

Commentary regarding aHUS International Poll results, by the aHUS Alliance: <http://bit.ly/1Q2UDZ2>

Infographic: <http://bit.ly/1Q2UHrA>

Resources – Learn More about aHUS

In ENGLISH: Disease OVERVIEW with definitions & research links

- NCBI GeneReviews[®], affiliated with the National Institutes of Health (NIH) <http://www.ncbi.nlm.nih.gov/books/NBK1367/>

In ENGLISH: Pediatric Focus

- An international consensus approach to the management of atypical hemolytic uremic syndrome in children, Abstract: <http://www.ncbi.nlm.nih.gov/pubmed/25859752>

Rare Diseases – Fast Facts

- There are approximately 7,000 diseases and conditions designated as a rare disease, each affecting fewer than 200,000 Americans. In Europe, a disease is considered rare if it affects fewer than 1 in 2,000 people.
- Rare diseases as a group affect an estimated 25 to 30 million Americans, 1 out of 10 people. Eighty percent of rare diseases are genetic in origin, and it is estimated that about half of all rare diseases affect children.

Information provided by:

EURORDIS: Founders of Global Rare Disease Day: Info & Resources www.eurordis.org

NORD: Rare Disease Day Info & Resources, specific to the USA www.rarediseases.org

RareConnect: Disease-Specific Webpages, sponsored by NORD and EURORDIS www.rareconnect.org

These organizations provide information, services, resources, and support to the rare disease community. Their Rare Disease Day resources include press kits, social media tools, Rare Disease Day graphics and more.



Rare Disease Day

World Rare Disease Day, recognized annually on the last day of February, encourages patients and their families, medical professionals, researchers, government officials, and companies developing treatments for rare diseases to join together to focus attention on rare diseases as a public health issue.

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